UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 7/21/99

SUBJECT: PP#: 7F3500 Tolerance Petition for the Residues of **Avermectin** in or on **Cotton Gin Byproducts**
Evaluation of Analytical Methodology and Residue Data

DP Barcode:	D254599	PRAT Case #:	281433
Submission No.:	S559247	Caswell #:	063AB
Chemical No.:	122804	Class:	Insecticide
Trade Name:	Zephyr 0.15 EC	EPA Reg No.:	100-897
40 CFR:	§180.449	MRID No.:	447085-05

TO: T. Harris/T. Levine, PM Team 04
MUIERB/RD (7505C)

FROM: Douglas Dotson, Chemist
RAB2/HED (7509C)

THROUGH: Y. Donovan and G. Herndon, Peer Reviewers
D. Davis, Branch Chief
RAB2/HED (7509C)

BACKGROUND

Novartis Crop Protection, Inc., has submitted a request to establish a tolerance for the combined residues of avermectin [≥80% avermectin B1a (5-O-demethyl avermectin A_{1a}) and ≤20% avermectin B1b (5-O-demethyl-25-de (1-methylpropyl)-25-(1-methylethyl) avermectin A_{1a})] and its delta-8,9-isomer in or on cotton gin byproducts at 0.15 ppm. Avermectin is currently registered for use on cotton. A time-limited tolerance of 0.005 ppm on cotton seed is in effect and is due to expire on 9/1/99.

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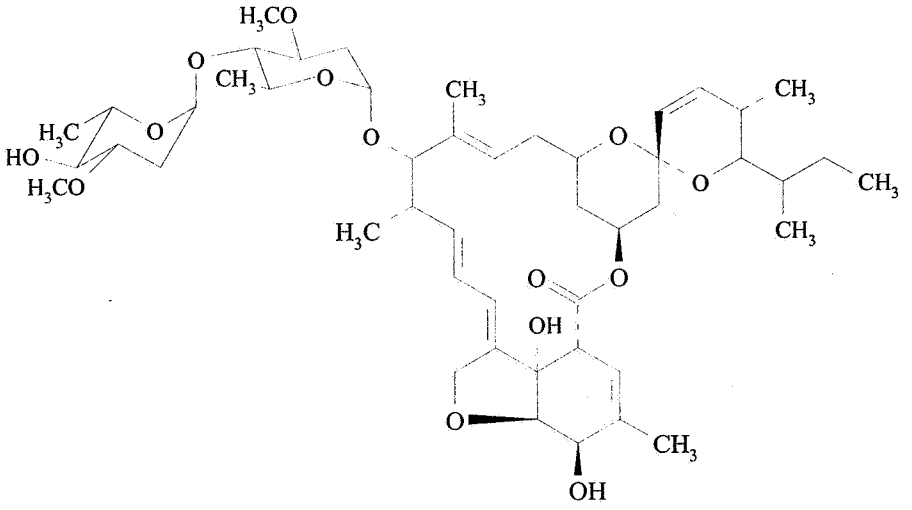
Tolerances are established under 40 CFR §180.449 for avermectin on various plant and animal commodities ranging from 0.005 ppm on almonds, cucurbits, and walnuts to a time-limited tolerance on dried hops at 0.2 ppm.

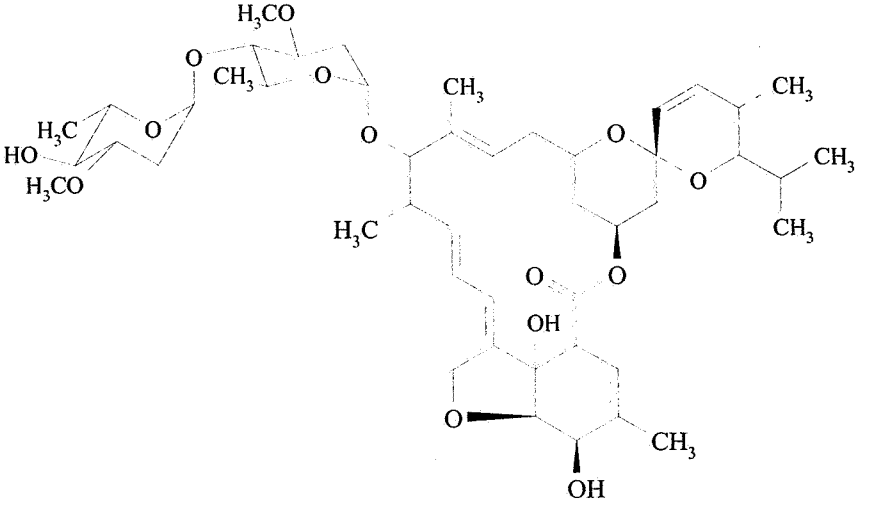
Avermectin is not a FIFRA '88 reregistration active ingredient.

The structures of Avermectin B1a and B1b are as follows:

Avermectin B1a



Avermectin B1b



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SUMMARY OF RESIDUE CHEMISTRY DEFICIENCIES

None

RECOMMENDATIONS

RAB2 recommends in favor of this petition for the establishment of permanent tolerances for residues of avermectin in cotton gin byproducts at 0.15 ppm. The addition of these residues to the diet of livestock commodities does not result in an increase in the residues present in animal commodities. Therefore the time-limited tolerances currently in effect for animal commodities are sufficient. Submission of a cotton gin byproduct study was the only outstanding data requirement which prevented HED from recommending that the animal commodity tolerances be made permanent. As this use of avermectin does not result in an increase in residues present in animal commodities, HED has no objection to converting the established time-limited tolerances for animal commodities to permanent tolerances.

HED previously recommended in favor of the establishment of a tolerance of 0.10 ppm for avermectin in wet apple pomace (Memo, G. Herndon, PP#4F4345, 5/2/95). This tolerance does not appear in 40 CFR §180.449. RD needs to establish this tolerance.

CONCLUSIONS

1. Product chemistry data were not submitted in conjunction with the subject petitions. The manufacturing process of technical avermectin has been adequately addressed. The end-use product, Zephyr 0.15 EC, contains 0.15 lbs ai/gallon as a mixture of avermectins containing ≥80% avermectin B1a and ≤20% avermectin B1b.

2. In the field trials that were performed to generate data for cotton gin byproducts the rates and PHIs which were used were similar to those outlined in the current Section 3 Zephyr label for cotton.

3. No new metabolism data were submitted with this petition. The nature of the residue in plants is adequately understood. The residues of concern are the parent compounds (avermectin B1a and B1b) and their delta-8,9-isomers (also referred to as (Z)-8,9-isomers).

4. The nature of the residue in ruminants is adequately understood. The residues of concern are the parent compounds (avermectin B1a and B1b) and their delta-8,9-isomers.

5. Avermectin has been subjected to testing under FDA multi-residue protocol methodology and cannot be recovered using any of the methods.

Method M-078, which is very similar to the registrant's method for hops (Method M-036.2) is adequate for enforcement purposes. Method M-036.2 has been validated by the Agency and submitted for inclusion in FDA's PAM II.

An analytical method for enforcing avermectin tolerances in bovine tissues and milk is available in PAM II.

6. Data reflecting the stability of avermectin in or on five crops during frozen storage have been submitted previously. Residues were stable in pears for one year; celery for two years; oranges, lemons, and grapefruits for one year; tomatoes for six months; and cottonseed (parent compound only) for 14 months. In this study, samples were stored frozen prior to analysis for a maximum of 5.3 months. RAB2 considers the previously submitted storage stability data to be adequate to support the analysis of avermectin in cotton gin byproducts.

7. The residue data on cotton gin byproducts submitted with this petition are adequate to support the proposed use. The highest residue found on cotton gin byproducts was 0.101 ppm. This level supports a tolerance of 0.15 ppm. The method was validated by fortifying control cotton gin byproduct samples and analyzing them concurrently with the treated and control samples. Average recovery of B1a was 93% and average recovery of B1b was 89%.

8. Based on the use of a reasonable animal diet, additional residues in cotton gin byproducts will not increase the dietary burden. Therefore the existing animal commodity tolerances are adequate to support the use of avermectin on cotton.

9. The requirements for rotational crop studies have previously been waived. No rotational crop data are required to support this action.

10. There are no Codex, Canadian, or Mexican MRLs for cotton gin byproducts.

DETAILED CONSIDERATIONS

Manufacture and Formulation

The manufacturing process of technical grade avermectin has been adequately described (Memo, L. Cheng, 5/1/86, EPA 618-OL). Zephyr 0.15 EC (EPA Reg. No. 100-897) contains 0.15 lbs ai/gallon (2.0 weight percent) as a mixture of avermectins containing ≥80% avermectin B1a and ≤20% avermectin B1b.

Proposed Use

Zephyr 0.15 EC is currently registered for use on cotton. Two applications may be made for a

total application rate of 0.0375 lb ai/A with a treatment interval of 21 days or more. The PHI is 20 days. Eight to sixteen fluid ounces of Zephyr per acre are to be used depending on the size of the plant and density of the foliage. Applications are to be made with ground sprayers or aerially by fixed-wing aircraft or helicopter in a minimum of five gallons of water per acre to provide thorough coverage. Applications are to begin when mites are first noticed. The product is not to be applied through any type of irrigation system and it is not to be applied east of the Mississippi River.

Nature of the Residue - Plants

No new plant or animal metabolism data were submitted with these tolerance requests. Metabolism data have been previously submitted on cottonseed, citrus, and celery (PP#'s 5G3500, 5G3287, and 8F3649, respectively). In addition, a report titled "Comparative Degradation of Avermectin B_1a in Cotton Leaf, Citrus Fruit, Celery, and In Vitro" was submitted in support of PP#9F3703 (reviewed by S. Willett, 12/15/89).

Previously, the metabolism components were examined from radio-labeled avermectin on celery (10 applications at 7 day intervals for a total equivalent of 1.0 lb ai/A/season), radio-labeled avermectin on cotton (3 applications at 50 to 89 day intervals for a total equivalent of 0.60 lb/A/season), and exaggerated application rates to citrus (30X, 2.25 lb ai/A). The residues of concern in/on these commodities were the parent compounds (avermectin B1a and B1b) and their delta-8,9-isomers (also known as (Z)-8,9 isomers).

RAB2's Comments/Conclusions

RAB2 concludes that the metabolism data are sufficient to support the recommended tolerance on cotton gin byproducts.

Nature of the Residue - Animals

Animal metabolism data were not submitted in conjunction with the subject petition. However, the metabolism of avermectin in goat and rat has been reviewed. From these studies, it was determined that the residues of concern in ruminants are avermectin B1a and B1b and their delta-8,9-isomers. This conclusion was based upon a feeding level of 1.0 mg/goat/day of ^{3}H-avermectin. An additional metabolite (24-hydroxymethyl avermectin B1a) was identified and is potentially of toxicological significance, but was not included in the tolerance expression because of its presence at low levels. However, RAB2 notes that if the livestock dietary burden is increased and the tolerances for residues in meat and milk need to be raised, then the 24-hydroxymethyl metabolite may need to be included in the tolerance expression and appropriate enforcement methods would need to be developed. Furthermore, an additional animal metabolism study using ^{14}C-avermectin would be needed if the expected ruminant dietary burden

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exceeded the dose level in the previously submitted goat metabolism study (see our memos of 6/21/89 and 11/26/91, F. Boyd, PP#8F3592/8H5550 and G. Herndon, 1F3973/1H5611, respectively).

Cotton gin byproducts are not a poultry feed item. Therefore a discussion of metabolism and secondary residues in poultry commodities is not pertinent to this petition.

RAB2's Comments/Conclusions

RAB2 concludes the available ruminant metabolism study is adequate to support the proposed tolerances for avermectin on cotton gin byproducts.

Analytical Methods

Avermectin has been tested using methodology described in PAM I, multi-residue method protocol A, which is the only applicable protocol. Avermectin is not recovered using the multi-residue methodology (Memo, G. Herndon, PP#4F4345, 5/2/95).

Residues of avermectin B1 and 8,9-Z avermectin B1 in cotton gin byproducts were determined using a modification of Method M-078. Samples are extracted with a methanol-water mixture. The avermectins are partitioned into hexane and the hexane extract is purified/concentrated on an NH_2 SPE column. The purified extract is derivatized with trifluoroacetic anhydride. The derivatized avermectins are analyzed by reversed phase HPLC with fluorescence detection. The avermectin B1a standard is used to calculate the concentration of avermectin B1a + 8,9-Z avermectin B1a and avermectin B1b + 8,9-Z avermectin B1b in/on the sample. The modifications made to Method M-078 included using a higher HPLC flow rate, preparing the standard solutions at different concentrations, centrifuging the samples with emulsions after shaking, and using equipment, apparatus, and chemical manufacturers which were different from those specified in the method. The limit of detection (LOD) is 1 ppb (0.001 ppm). The limit of quantitation is 2 ppb. The method was validated by fortifying control gin trash samples and analyzing them concurrently with the treated and control samples.

Method M-078 is very similar to the registrant's method for hops, Method M-036.2, which has been submitted for inclusion in FDA's PAM II (Memo, W. Wassell, PP#5E4556, 6/11/96). As the two methods are very similar and method recovery was good, RAB2 considers Method M-078 to be adequate for enforcement purposes.

Merck Method 32A is available for enforcing avermectin tolerances in bovine tissues and milk. This method has been published in PAM II (Method II).

RAB2's Comments/Conclusions

RAB2 concludes that adequate analytical methodology is available for enforcement of the proposed tolerance on cotton gin byproducts and the established tolerances on ruminant commodities.

Storage Stability

Data reflecting the stability of the avermectins in or on five crops during frozen storage have been submitted previously. Residues were stable in pears for one year (Memo, J. Stokes, PP#9F3787, 7/9/91); celery for two years (Memo, S. Willett, PP#8F3649, 5/4/90); oranges, lemons, and grapefruits for one year (Memo, V. F. Boyd, PP#8F3592, 6/21/89); tomatoes for six months (Memo, S. Willett, PP#9F3703, 12/15/89); and cottonseed (parent compound only) for 14 months (C. Deyrup, PP#7F3500, 7/29/87). In this study, samples were stored frozen prior to analysis for a maximum of 5.3 months. RAB2 considers the previously submitted storage stability data to be adequate to support the cotton gin byproduct analyses.

Magnitude of the Residue - Crop Field Trials

Eight field trials were conducted in five different states. The cotton produced in these states accounted for approximately 50% of the total upland cotton produced in the United States in 1995. These states and the number of field trials conducted in each are as follows: South Carolina (1 trial), Arkansas (1 trial), Oklahoma (1 trial), Texas (3 trials), and California (2 trials). Cotton was grown under normal agricultural conditions. Abamectin 0.15 EC (emulsifiable concentrate) was applied at a rate of 0.019 lb. a.i./acre to cotton twice with a spray interval of 17-21 days. The second (final) application was made when approximately 30%-90% of the bolls were open. The application rate used is equivalent to the maximum rate allowed on the label (i.e., a 1x application rate was used). Seed cotton was harvested 25-30 days after the last application using either a spindle harvester (mechanical picker) or a stripper harvester. In four of the trials a mechanical picker was used and in the other four trials a stripper harvester was used. Samples were shipped frozen from the test sites to the Food Protein R&D Center of the Texas A&M University System in Bryan Texas for processing (ginning). Processing procedures simulated normal commercial procedures as closely as possible. Gin trash samples were shipped from the Food Protein R&D Center to MVTL Laboratories in New Ulm, Minnesota for sample preparation and analysis. Sample preparation of the gin trash samples was performed according to the procedures outlined in Method of Analysis M-078. Samples were stored frozen at MVTL, with subsamples removed for analysis. Residues of avermectin B1 and 8,9-Z avermectin B1 were determined by MVTL using Method M-078. The limit of detection of the method was 0.001 ppm. The limit of quantitation was 0.002 ppm. The results of the analyses are given in Table 1. The value reported for B1a includes both the parent and 8,9-Z isomer. The same is true for B1b. The reason the parent and isomer are reported together is that prior to analysis, purified sample extracts are derivatized to common moieties.

Table 1. Residues of Avermectin in/on Cotton Gin Byproducts						
Location Trial Number	Method of Harvest	Treatment Rate (lb ai/A)	PHI (days)	Residue Level (ppb)		
				B1a + 8,9-Z isomer	B1b + 8,9-Z isomer	B1a + B1b (+ isomers)
South Carolina 01-IR-013-97	Spindle Harvester	Control	-	<2	<2	<2
		2 x 0.019	25	29	2	31
				28	2	30
Arkansas 01-IR-014-97	Spindle Harvester	Control	-	<2	<2	<2
		2 x 0.019	25	7	<2	7
				6	<2	6
Oklahoma 01-IR-015-97	Stripper Harvester	Control	-	<2	<2	<2
		2 x 0.019	25	7	<2	7
				5	<2	5
Texas 01-IR-016-97	Stripper Harvester	Control	-	<2	<2	<2
		2 x 0.019	25	3	<2	3
				3	<2	3
Texas 01-IR-017-97	Stripper Harvester	Control	-	<2	<2	<2
		2 x 0.019	25	16	<2	16
				16	<2	16
Texas 01-IR-018-97	Stripper Harvester	Control	-	<2	<2	<2
		2 x 0.019	25	4	<2	4
				4	<2	4
California 01-IR-019-97	Spindle Harvester	Control	-	<2	<2	<2
		2 x 0.019	25	26	<2	26
				32	<2	32
California 01-IR-020-97	Spindle Harvester	Control	-	<2	<2	<2
		2 x 0.019	25	85	6	91
				94	7	101

The method was validated by fortifying control gin byproduct samples and analyzing them concurrently with the treated and control samples. Control samples were fortified with avermectin B1a at levels of 2 ppb, 10 ppb, 50 ppb, and 100 ppb. These levels bracket the residue levels of B1a found in the residue samples. Similarly, control samples were fortified with avermectin B1b at levels of 3.4 ppb and 6.8 ppb. These levels are consistent with the levels of B1b found in the residue samples. Results of the recovery analyses are given in Table 2. Recoveries of B1a ranged from 84% to 106%, with an average of 93% (n=8). Recoveries of B1b ranged from 79% to 99%, with an average of 89% (n=4).

Table 2. Procedural Recoveries of Avermectin B1a and B1b from Fortified Controls of Cotton Gin Trash			
Location Trial Number	**Fortification Level (ppb)**	**Recovery (%)**	
		B1a	**B1b**
South Carolina 01-IR-013-97	2	84	-
Arkansas 01-IR-014-97	10	90	-
Oklahoma 01-IR-015-97	50 3.4	93 -	- 99
Texas 01-IR-016-97	100 6.8	85 -	- 82
Texas 01-IR-017-97	2 2	106 89	- -
Texas 01-IR-018-97	10	103	-
California 01-IR-019-97	50 3.4	84 -	- 79
California 01-IR-020-97	100 6.8	95 -	- 94
	Average	92	89
	Standard Deviation	8	10
	n	9	4
	Range	84-106	79-99

RAB2's Comments/Conclusions

The petitioner has submitted the results of eight field trials for avermectin in/on cotton gin byproducts. OPPTS Test Guidelines Series 860 requires that a minimum of six field trials be performed: three by stripper and three by mechanical picker. RAB2 concludes that this requirement has been satisfied. The highest residue level obtained (sample 01-IR-020-97) was 0.101 ppm. The avermectin application rate was 1x. The PHI was slightly longer than that specified on the label, however. The label specifies a PHI of 20 days. The PHI used in the field trails was 25 days. RAB2 feels that the field trial use pattern and residue levels support a tolerance of 0.15 ppm. Adequate method recovery data have been submitted. As a result, RAB2 recommends in favor of the establishment of a tolerance of 0.15 ppm for the residues of avermectin in/on cotton gin byproducts. The establishment of this tolerance is not dependent on

the results of a human health risk assessment as animal commodity tolerances will not be affected by the establishment of this tolerance.

Magnitude of the Residue in Meat, Milk, Poultry and Eggs

Cotton gin byproducts are not a feed item for poultry or swine, therefore these commodities will not be addressed in this review.

Cotton gin byproducts can comprise up to 20% of the diets of both beef and dairy cattle. According to Table 1 of the OPPTS Test Guidelines Series 860 the following animal feed items are associated with commodities with avermectin registrations: almond hulls, wet apple pomace, dried citrus pulp, cotton seed, potato culls, and potato waste. Of these commodities, cotton seed meal is the only highly nutritive one. The others mainly provide fiber to the diet. Cotton seed meal will be distributed to all parts of the country, but the others will not. Therefore it is reasonable to construct a dietary burden with cotton seed meal and only one of the other "esoteric" feed items. Wet apple pomace would contribute the highest residues to the diet, therefore a dietary burden was constructed using cotton seed meal and apple pomace. This dietary burden is given in Table 3.

Table 3. Avermectin Theoretical Dietary Burdens for Beef and Dairy Cattle

Commodity	Tolerance (ppm)	%DM	Percent of Livestock Diet		Contribution to Dietary Burden (ppm)	
			Beef	Dairy	Beef	Dairy
Wet Apple Pomace	0.10	40	40	20	0.10	0.05
Cotton Seed	0.005	88	25	25	0.0014	0.0014
Total			65	45	**0.101**	**0.051**

Table 4 gives the established tolerances as well as the residues found in tissues and milk of dairy cattle fed 0.10 ppm avermectin (Memo, L. Cheng, PP#7G3468, 2/11/87).

Table 4. Avermectin: Established Tolerances and Residues in Tissues and Milk from Cattle Fed 0.10 ppm Avermectin

	Liver (ppm)	Muscle (ppm)	Fat (ppm)	Kidney (ppm)	Milk (28-day) (ppm)
Residue	0.019	0.002	0.012	0.004	0.002

Table 4. Avermectin: Established Tolerances and Residues in Tissues and Milk from Cattle Fed 0.10 ppm Avermectin					
	Liver (ppm)	**Muscle (ppm)**	**Fat (ppm)**	**Kidney (ppm)**	**Milk (28-day) (ppm)**
Established Tolerance	0.020	0.020	0.015	0.020	0.005

The feeding study was done at 3 different feeding levels: 0.010 ppm, 0.030 ppm, and 0.10 ppm. The dietary burden constructed with cotton seed and apple pomace is essentially the same as the highest feeding level: 0.10 ppm. The established tolerances are adequate to cover this dietary burden. As the tolerances will not change, it is not necessary to perform a dietary exposure analysis.

In the dietary burden calculation a tolerance of 0.10 ppm was used for wet apple pomace. This tolerance does not appear in 40 CFR §180.449. HED recommended in favor of the establishment of this tolerance (Memo, G. Herndon, PP#4F4345, 5/2/95). A tolerance of 0.10 ppm needs to be established for the residues of avermectin in wet apple pomace.

RAB2's Comments/Conclusions

RAB2 concludes that when a reasonable dietary burden is constructed using wet apple pomace and cotton seed, that residues present in animal commodities will not increase over current levels. Therefore, it is not necessary to increase the established tolerances for animal commodities.

Rotational Crops

No rotational crop studies were received with this submission. Review of the results of the confined rotational crop study indicated that avermectin residues accumulated in some rotational crops at levels up to 10 - 12 ppb. However, the radioactivity was due to polar degradates that were of little toxicological concern as compared to the parent compound avermectin B1 and/or the delta-8,9-isomer (see memo of P. Mastradone dated 4/24/88). Therefore, the requirements for field rotational crop studies have been waived (PP#7F3500, #8F3592, and #5E4566, DP Barcodes: D230333, D230352, D230880, G. Herndon, 1/10/97).

International Harmonization of Tolerances

There are no Codex, Canadian, or Mexican maximum residue limits (MRL) for avermectin in cotton gin byproducts. Therefore, international harmonization is not an issue for cotton gin byproducts. A Codex MRL has been established for cotton seed: 0.01 ppm. This MRL differs from the time-limited tolerance currently in effect for cotton seed: 0.005 ppm.

Attachment: International Residue Limit Status Sheet
RDI: Y. Donovan and G. Herndon: 7/8/99, D. Davis: 7/16/99

cc: D. Dotson, PP# 7F3500